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TED APPLE (TOWNSEND AND TOWNSEND AND CREW)  
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EXAMINER

ROBINSON, HOPE A

ART UNIT PAPER NUMBER

1656

DATE MAILED: 08/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

10/672,396

Applicant(s)

SANTI ET AL.

Examiner

Hope A. Robinson

Art Unit

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 20 March 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-56 and 69-76 is/are pending in the application.
- 4a) Of the above claim(s) 16-23, 25-38 and 40-56 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-15, 24, 39 and 69-76 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 April 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 3/31/06; 3/20/06; 11/12/04
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other Notice to Comply

## **DETAILED ACTION**

### ***Application Status***

1. Applicant's election with traverse of Group I (claims 1-15, 24, 39 and 62) is acknowledged.
  
2. The traversal is on the grounds that all inventions should be searched as there is no search burden. Applicant's arguments indicate that search burden is removed because a search was conducted on a PCT with similar claims. Applicant's also provided a discussion of the references cited in an attempt to argue that unity of invention is present. This argument is not persuasive. The PCT application in question was found to lack unity and applicant's paid for the entire application to be searched. Moreover, the instant application is not a national stage to the PCT referred to and Restriction Practice is separate from PCT Lack of Unity Practice. Thus arguments presented using the PCT is not germane to Restriction Practice. In addition, MPEP chapter 800 indicates that Restriction Requirement is proper if the claimed invention is independent and/or distinct. Further, burden of search is established based on the separate classification, which demonstrates that the claimed invention has not acquired the same status in the art, and that the search is not coextensive. Thus, the restriction requirement is deemed proper and is final.

### ***Claim Disposition***

3. Claims 57-68 have been canceled. Claims 69-76 have been added. Claims 1-56 and 69-76 are pending. Claims 1-15, 24, 39 and 69-76 are under examination. Claims 16-23, 25-38 and 40-56 are withdrawn from further consideration pursuant to 37 CFR 1.12(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Claims 24 and 39 are only being examined to the extent that they pertain to the elected subject matter.

4. The Amendment filed on September 29, 2005 has been received and entered.

### ***Specification***

5. The specification is objected to because of the following informalities:

(a) The specification is objected to because trademarks are disclosed throughout the instant specification and not all of them are capitalized or accompanied by the generic terminology. The use of the trademarks such as FIAGS<sup>TM</sup>, for example, have been noted in this application (see page 113). It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks. It is suggested that applicant review the lengthy specification for other trademarks that may not be in proper form.

(b) The specification is also objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See pages 20, 26 and 83 for example. It is suggested that http:// is deleted.

(c) The specification is objected to because the "Brief Description of the Drawing" section does not adequately describe several figures. For example, Figure 1B and Figure 2 display sequences, however, no sequence identifier is present. In addition, Figure 9 and Figure 18 have parts "A and B", however, the description does not mention these.

Correction is required.

### ***Sequence Compliance***

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicant is required to identify all amino acid sequences of at least 4 L-amino acids and at least 10 nucleotides by a sequence identifier, i.e., "SEQ ID NO:". The specification discloses sequences that have not been identified by a sequence identifier, see for example, page 90: see Table 7; the sequence EPIAIV and YXFXXRXW (where X is any amino acid). In addition, Figures 1B and 2 disclose

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sequences which have not been identified with sequence identifiers. If these sequences have not been disclosed in the computer readable form of the sequence listing and the paper copy thereof, applicant must provide a computer readable form of the "Sequence Listing" including these sequences, a paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable form copies are the same and, where applicable, include no new matter as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See the attached Notice to Comply with the sequence rules.

### ***Drawing***

7. The drawings filed on April 16, 2004 have been accepted by the examiner.

### ***Information Disclosure Statement***

8. The Information Disclosure Statements filed on March 31, 2006, March 20, 2006 and November 12, 2004 have been received and entered. The references cited on the PTO-1449 Form have been considered by the examiner and a copy is attached to the instant Office action.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-15, 24, 39 and 69-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a synthetic gene encoding a polypeptide segment that corresponds to a reference polypeptide (see for example claim 1), however, the claims do not set forth said "reference polypeptide" and are devoid of a structure. In addition, no functional limitation is recited in the claims for the recited "polypeptide segment", thus no correlation is made between function and structure. It is noted that claim 2 recites a PKS polypeptide segment, however, there is no indicia as to what said segment looks like or the reference structure. Further, the claimed invention is directed to a coding segment of the gene that is less than about 90% or 85% or 80% or 70% of the naturally occurring gene". Thus, the claims encompass a large variable genus, not adequately described. The skilled artisan cannot envision the detailed chemical structure of the genus encompassed in the claims, thus the claimed invention lacks adequate written description.

The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for

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a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The claimed genus could include non-functional proteins or proteins with a different function than the one contemplated. Therefore, the genus of claimed polypeptides encompasses widely variant species. Based on the unlimited variations contemplated one skilled in the art would at best expect a protein that is different or at worst a protein that is not functional. Further, *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has



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occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

*See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

10. Claims 1-15, 24, 39 and 69-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification is not enabled for the full scope of the claims, for example, the specification does not reasonably provide enablement for any segment of the polypeptide or variant/fragment thereof recited peptide in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and

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Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)). The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass a large variable genus of polypeptide segments and nucleic acid segments encoding said polypeptide. Note that the claims are directed to a synthetic gene encoding a polypeptide segment that corresponds to a reference polypeptide, however, the claims do not set forth said "reference polypeptide" and are devoid of a structure. In addition, no functional limitation is recited in the claims for the recited "polypeptide segment" to correlation a structure with function. It is noted that claim 2 recites a PKS polypeptide segment, however, there is no indicia as to what said segment looks like or the reference structure. Further, the claimed invention is directed to a coding segment of the gene that is less than about 90% or 85% or 80% or 70% of the naturally occurring gene". Thus, the claims encompass a large variable genus, not adequately described. Due to the large quantity of experimentation necessary to generate the infinite number of variants/fragments recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, *Biochemistry*, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity

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comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. For example, Tuddenham et al. (Nucleic Acids Research, vol. 22, no. 17, pages 3511-3533, 1994) discloses an established database of nucleotide substitutions, deletions, insertions and rearrangements. The database demonstrates the deleterious impact that various point mutations, deletions and insertions have on the function of a Factor VIII protein. Furthermore, Tuddenham et al. demonstrates that a change of only a single nucleotide may result in loss of function in the protein product (see page 3512 of the reference). Therefore, the art speaks to the high degree of unpredictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity. The art also demonstrates that detailed knowledge of the ways in which the protein's structure relates to its function is necessary hence the need for exemplification or guidance/direction in the instant specification.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining

similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed modifications in the gene and the protein product. The nature and properties of this claim is difficult to ascertain from the examples provided, as one of skill in the art would have to engage in undue experimentation to construct the variants of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of variants/fragments for the gene and the gene product. The claims broadly read on any structure and function is not supported by the instant specification. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the

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specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 1-15, 24, 39 and 69-76 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

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Claims 1, 7, 75 and the dependent claims hereto are indefinite for the recitation of "a polypeptide segment that corresponds to a reference polypeptide", as it is unclear what "reference polypeptide" is being referred to because no structure is recited in the claims.

Claim 14 lacks clear antecedent basis for the recitation of "said PKS" because this acronym is not recited in the independent claim.

Claim 24 is incomplete, as the claim recites material that is not elected subject matter, thus the claim is confusing because it is not clear what "R1" is and how it pertains to the claimed invention as a whole.

Claim 39 lacks clear antecedent basis for the recitation of "The method of claim 1", because claim 1 is a product claim. In addition, the claim is confusing as non-elected subject matter appears in the claim, which renders the claim as incomplete.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1 and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Wingfield, et al. (Protein Science, 1997, vol. 6, pages 1653-1660, cited on IDS).

Wingfield et al. teach a DNA encoding a mutated protein (protein segment, i.e. residues 27-149 or residues 1-149 of a transmembrane glycoprotein) of gp41 from

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SIVmac239 (see pages 1653-1654 of the reference). The claimed invention is directed to a gene that is less than about 90% identical to the polypeptide encoding sequence of the naturally occurring gene, which is anticipated by the reference. The specification does not define the range of "about". The art recognizes the term 'about' to be extendable to a range of  $\pm 10$  thus, about 90% can be interpreted as "80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100%". Therefore, less than about 90% can be any percent approaching 80%, which, means 99%, or 98% meets this limitation. Based on the range encompassed in the claims the cited reference teaching mutations would achieve a percentage in this range. Therefore, the limitations of the claims are met by the reference.

13. Claims 1-4, 7 and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by ABBOTT LABORATORIES (WO 93/13663, 22 July 1993, cited on IDS).

ABBOTT LABORATORIES teach a modified DNA encoding a polyketide and polyketide analogs (see abstract). In addition, ABBOTT LABORATORIES teach ACP, ER, KR among other PKS domains and modules (see pages 3 and 32 of the reference. The claimed invention is directed to a gene that is less than about 90% identical to the polypeptide encoding sequence of the naturally occurring gene, which is anticipated by the reference. The specification does not define the range of "about". The art recognizes the term 'about' to be extendable to a range of  $\pm 10$  thus, about 90% can be interpreted as "80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100%". Therefore, less than about 90% can be any percent approaching 80%.



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Based on the range encompassed in the claims the cited reference teaching mutations would achieve a percentage in this range. Therefore, the limitations of the claims are met by the reference.

14. Claims 1 and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Mandecki et al. (Gene, 1988, vol. 68, pages 101-107, cited on IDS).

Mandecki et al. a synthetic gene and gene fragments encoding an N-terminal HIV transmembrane protein (p41). The reference teaches the cleavage of at least one of four restriction sites and that restriction sites are not required in said gene (see page 101 of the reference). The claimed invention is directed to a gene that is less than about 90% identical to the polypeptide encoding sequence of the naturally occurring gene, which is anticipated by the reference. The specification does not define the range of "about". The art recognizes the term 'about' to be extendable to a range of  $\pm 10$  thus, about 90% can be interpreted as "80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100%". Therefore, less than about 90% can be any percent approaching 80%. Based on the range encompassed in the claims the cited reference teaching mutations would achieve a percentage in this range. Therefore, the limitations of the claims are met by the reference.

**Conclusion**

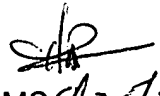
15. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday from 9:00 a.m. to 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Hope Robinson, MS 8/28/06

Patent Examiner

**HOPE ROBINSON**  
**PATENT EXAMINER**

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other:

**8. Applicant Must Provide:**

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g).

For questions regarding compliance to these requirements, please contact:

- For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
- For CRF Submission Help, call (703) 308-4212
- For PatentIn software Program Support:
  - HELP DESK: (703) 739-8559, ext 508, M-F, 8 AM to 5 PM EST except holidays
  - Email: [PATIN21HELP@uspto.gov](mailto:PATIN21HELP@uspto.gov)
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